Haj-Yehia, Abdullah I.

10/512,024

__3__

1. (Currently Amended) A multifunctional β -agonist compound being ROS scavenger and NO donor of Formula 1:

$$R^3$$
 R^4
 R^5

or its salt or a solvate thereof or an optical isomer thereof, wherein R¹ is -SNO;

 R^2 is ROS scavenger group or a NO donor group connected to the -NH group via a linker made of C_5 - C_8 cyclic alkyl, or straight or branched C_1 - C_{15} alkyl in which one carbon atom is optionally replaced by oxygen or nitrogen, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from -ONO, -ONO₂, -SNO, and -NONOate or R^2 is C_5 - C_8 cyclic alkyl, or straight or branched C_1 - C_{15} alkyl;

R³ and R⁴ together form a substituted 5 to 7-membered saturated heterocycle having 1 or 2 heteroatoms independently selected from nitrogen, and oxygen, and sulfur, wherein one of said nitrogen atoms being optionally substituted by oxygen to form a nitroxide radical;

 R^5 is selected from the group consisting of -H and straight or branched chain C_1 - C_{15} alkyl;

Haj-Yehia, Abdullah I.

10/512,024

4

and whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, bromo, fluoro, chloro, iodo, mercapto exthio, cyano, alkylthio, aryl, carboxyl, carbalkoyl, alkenyl, nitro, amino, alkoxyl, or amido;

wherein at least one of R¹, R², R³ and R⁴ comprises at least one is said ROS scavenger if said saturated heterocycle does not have the nitrogen atom substituted by oxygen selected from the group of moieties consisting of a nitroxide free radical, alkenyl, sulfhydryl ordithiol in oxidized or reduced form, and aryl, and

wherein one or more of R¹, R², R³-and R⁴-comprise at least one NO-donor selected from -ONO, -ONO₂, and -SNO.

- 2. (Original) A β -agonist compound according to claim 1, wherein said saturated heterocycle is selected from the group consisting of pyrrolidine, oxazolidine, thiazolidine, tetrahydro 1,3-oxazine, 1,3-dioxane, piperidine, 3-thiapiperidine, and 1,3-thiazine.
- 3. (Canceled) A β agonist compound according to claim 2, wherein said saturated heterocycle comprises a substituted nitroxide free radical.
- 4. (Currently Amended) A β -agonist compound according to claim $\underline{1}$ 3, wherein the nitroxide free radical is a heterocyclyl moiety having the nitrogen atom within a 5-, 6- or 7-membered ring which optionally contains another heteroatom selected from oxygen and sulfur at position beta

Haj-Yehia, Abdullah I.

10/512,024

__5_

to the nitrogen, and which is substituted with methyl or ethyl at positions alpha to the nitrogen.

- 5. (Original) The β -agonist compound of claim 4, wherein said heterocyclyl moiety is linked to the β -agonist moiety via sharing of 1 to 2 atoms, or via a linker.
- 6. (Original) A β -agonist compound according to claim 1, wherein said ROS scavenger group is selected from the group consisting of the following moieties:

wherein X is selected from carbon, oxygen, and sulfur, and n is an integer from 1 to 15.

Haj-Yehia, Abdullah I.

10/512,024

--6--

7. (Original) A β -agonist compound according to claim 1, wherein R^2 is selected from the following structures:

Haj-Yehia, Abdullah I.

10/512,024

___7__

wherein m is 1 -6 and R 8 and R 9 are independently C $_{1}\text{-}\text{C}_{3}$ alkyl or -H.

8. (Currently Amended) A β -agonist compound according to claim 1 having the formula:

or its salt of a solvate thereof or an optical isomer thereof; wherein R¹ is -SNO;

R⁵ is hydrogen; and

Haj-Yehia, Abdullah I.

10/512,024

--8--

 R^2 is a moiety selected from a nitroxide free radical having the nitrogen atom within a 5-, 6- or 7-membered saturated ring and which is substituted by up to four methyl groups at positions alpha to the nitrogen, sulfhydryl or dithiol moiety in oxidized or reduced form,—ONO, —ONO₂, and —SNO, wherein said moiety is connected to the —NH group directly or via a linker made of C_1 - C_6 alkyl, and which linker is

optionally substituted by one or more phenyl groups.

9. (Currently Amended) A multifunctional β -agonist compound according to claim 1 having one of the following structures:

$$0.-N$$

$$1$$

$$0.-N$$

$$0.-$$

Haj-Yehia, Abdullah I.

10/512,024

__9__

10. (Canceled)

11. (Canceled)

12. (Withdrawn) A process of preparing an agonist according to claim 1 being a compound of the formula:

or its salt, wherein R¹ is -SNO;

 R^2 is ROS scavenger group or a NO donor group connected to the -NH group via a linker made of C_5 - C_8 cyclic alkyl, or straight or branched C_1 - C_{15} alkyl, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moëty in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from -ONO, -ONO₂, and -SNO or R^2 is C_5 - C_8 cyclic alkyl, or straight or branched C_1 - C_{15} alkyl;

and R^5 is selected from the group consisting of -H and straight or branched chain $C_1 - C_{15}$ alkyl;

Inventor: Haj-Yehia, Abdullah I.

Serial no.: 10/512,024

--10---

and whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, and alkoxyl;

which process comprises reacting a chiral or nonchiral epoxide or thioepoxide of the formula

$$O - N$$
 R_5

with an amine of the formula H_2N-R^2 wherein Z is oxygen or sulfur;

 R^2 is a C_5 - C_8 cyclic alkyl, or straight or branched C_1 - C_{15} alkyl linked to a group selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, aryl, -ONO, $-ONO_2$, and -SNO; wherein said alkyl is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, alkoxyl, C_1 - C_5 alkyl, C_1 - C_5 alkoxy, phenyl, and $-CH_2OH$;

and R^5 is selected from the group consisting of -H and straight or branched chain $C_1 - C_{15}$ alkyl.

13. (Withdrawn) A process according to claim 12, wherein said epoxide is prepared from N-benzylphthalimide.

Inventor: Haj-Yehia, Abdullah I.

Serial no.: 10/512,024

---11---

14. (Withdrawn) A process according to claim 12, further comprising converting -SH groups to -SNO groups in the presence of HCl and $NaNO_2$.

- 15. (Withdrawn) A composition comprising a multifunctional β -agonist compound of claim 1, or a salt thereof or a solvate thereof or an optical isomer thereof, for use as a medicament.
- 16. (Withdrawn) A method of treating or preventing a respiratory disorder in a mammal in need thereof comprising administering to said mammal an effective amount of a multifunctional β -agonist compound of any one of claims 1 to 9, or a salt thereof or a solvate thereof or an optical isomer thereof.
- 17. (Withdrawn) A method according to claim 16, wherein said disorder is selected from the group consisting of asthma, chronic bronchitis, bronchiectasis, emphysema, chronic obstructive pulmonary disease, chronic obstructive airway disease, acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) in child or adult, pneumonia, pneumonitis, and restrictive diseases of the lungs.
- 18. (Withdrawn) A method according to claim 16, comprising symptoms selected from the group consisting of recurrent obstruction to air flow within the lung, increased resistance to air flow, narrowing or restriction of an airway, inflammation, bronchial hyperreactivity, airway

Inventor: Haj-Yehia, Abdullah I.

Serial no.: 10/512,024

-12--

hyperresponsiveness, mucosal edema, mucus plugging and hypersecretion, and reduced expansion of respiratory parenchyma.

- 19. (Withdrawn) A method according to claim 17, wherein said asthma is selected from the group consisting of atopic, extrinsic, and intrinsic.
- 20. (Withdrawn) A method according to claim 16, wherein said administration is selected from the group consisting of systemic administration and topical administration.
- 21. (Withdrawn) A method according to claim 16, wherein said β -agonist compound is administered by a route selected from the group consisting of oral, parenteral, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, implant, buccal, inhalation spray, nasal, vaginal, rectal, and sublingual route.
- 22. (Withdrawn) A method of claim 16, wherein said mammal is human.
- 23. (Original) A pharmaceutical composition comprising a β -agonist compound of any one of claims 1 to 9, or a salt thereof or a solvate thereof or an optical isomer thereof.
- 24. (Original) A pharmaceutical composition according to claim 23, further comprising carriers, adjuvants, and excipients.

Haj-Yehia, Abdullah I.

10/512,024

—13—

25. (Canceled) A pharmaceutical composition-according to elaim 23, further comprising an active agent selected from the group consisting of mucolytic, bronchodilator, muscle relaxant, decongestant, respiratory stimulant, vasodilator, β agonist, antiallergic, antiasthmatics, analgesic, anti-inflammatory, antibiotic, antifungal, antiprotozoal, and antiviral agent.

- 26. (Withdrawn) A method according to claim 21, wherein said administration is via an inhalation device.
- 27. (Withdrawn) An inhalation device for administering a multifunctional β -agonist compound or its salt according to claim 1.
- 28. (Withdrawn) A kit comprising an inhalation device according to claim 27, in which said multifunctional β -agonist is in the form of fine power or solution or suspension, wherein said powder or solution or suspension optionally contains other components selected from bulking agent, buffer, carrier, excipient, additive, antioxidant, stabilizer, surfactant, odorant, and a second pharmaceutically active agent.